

Stein-Leventhal Syndrome*

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The syndrome described in 1935 by Stein and Leventhal is "characterized by secondary amenorrhoea, sterility, bilateral polycystic ovaries and hirsutism occurring in young women in the second or third decades of life" (Leventhal, 1958). Our paper presents a study of 30 patients, some of whom were typical of the Stein-Leventhal syndrome while others differed from this syndrome in several respects. Most of the patients had hirsutism, oligomenorrhoea, or amenorrhoea, and in all but three of the series wedge resection of the ovaries was followed by regular menstruation.

Present Series

Age and Parity.—Table I shows that most of the patients were in their late teens or early twenties. Sixteen of the 30 were married and all were nulliparous.

TABLE I.—Age of Patients at Presentation

| Age | <15 | 15-19 | 20-24 | 25-29 | 30-34 |
|-----------------|-----|-------|-------|-------|-------|
| No. of patients | — | 2 | 14 | 9 | 5 |

History.—The presenting symptoms were: Absent or infrequent periods, 21; hirsutism, 11; infertility, 7; obesity, 3. The menarche occurred at the normal age and the menstrual cycle was apparently normal for several years. In later adolescence the interval between the periods lengthened. On questioning it was possible to assess the duration of the patient's symptoms and to arrive at the approximate age of onset of the condition (Table II).

TABLE II.—Age at Onset of Major Complaint

| Age | <15 | 15-19 | 20-24 | 25-29 | 30-34 |
|-----------------|-----|-------|-------|-------|-------|
| No. of patients | 11 | 9 | 7 | 3 | 0 |

Physical Features.—Hirsutism was evident in 27 of the patients and was sufficiently marked for 13 of them to shave, seven daily. All those with increased facial hair had more profuse hair on the limbs, and in 15 patients the pubic hair was of male distribution. Only four of the 30 patients had small breasts; this contrasts with Stein's (1959) series, where "half the patients had breasts smaller than usual." Obesity was present in nine patients. Pelvic examination was sometimes difficult because of the thickness of the abdominal wall, and enlarged ovaries were felt in only nine patients. Assessment of the size of the ovaries by bimanual palpation is not entirely reliable, especially if the patient is fat. The uterus was usually of normal size, and this finding was confirmed by measurement of the cavity before curettage. Again this differs from Stein's (1959) group, where 75% had hypotrophic uteri.

Investigations

Urinary Hormone Excretion.—The urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids was in the normal range in more than half of the patients (Fig. 1), but was signifi-

cantly increased in seven. The results did not indicate any marked degree of adrenocortical hyperfunction. The urinary excretion of gonadotrophins of pituitary origin was above the normal range in five of the 18 patients in whom the assay was performed. Cox and Shearman (1961) and M. I. Stern and J. O. H. Barwell (personal communication, 1962) have found elevated levels of urinary Δ^5 -triol (pregn-5-en-3 β , 17 α , 20 α -triol) in patients with the Stein-Leventhal syndrome.

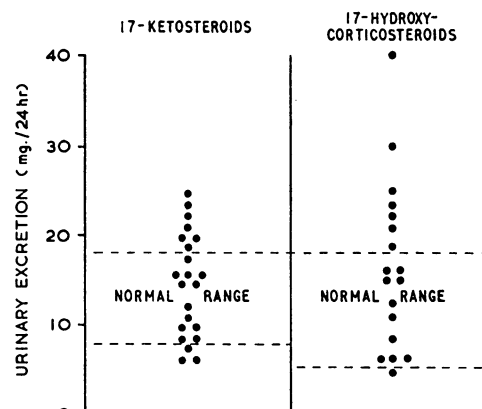


FIG. 1.—Urinary hormone excretion in patients in this series.

Endocrine Vaginal Cytology.—Serial cytology was studied in 18 of the patients, all of whom subsequently responded to wedge resection of the ovaries. The smears showed a marked hormonal activity of a mixed oestrogen/androgen/progesterone pattern in both the amenorrhoeic and the follicular phase of the oligomenorrhoeic. When ovulation occurred the picture was masked by androgen, but after ovulation the androgenic influence disappeared and the luteal phase was indistinguishable from that of a normal ovulatory cycle (Fig. 2). The typical oestrogenic smear was never seen, the cornification index being less than 20 except in the luteal phase, when it sometimes reached 30. There was an excessive and persistent secretion of cervical mucus which is thought to be characteristic of the Stein-Leventhal syndrome.

Culdoscopy.—Visual examination of the ovaries may be performed by peritoneoscopy or culdoscopy, and the latter

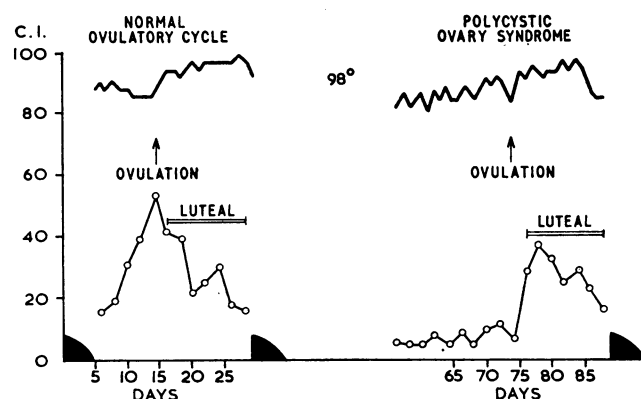


FIG. 2

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procedure was carried out on 14 of the patients. Assessment of the size of the ovaries by culdoscopy is not always reliable, but the procedure sometimes aids the diagnosis when pelvic assessment is difficult.

Treatment

Two types of treatment are available to the patient with the Stein-Leventhal syndrome—surgery or hormone therapy. The latter has been favourably reported (Greenblatt *et al.*, 1956) using either cortisone or a combination of oestrogen and cortisone. In four patients in the present series prednisolone therapy was used for several months without success, and in a fifth the treatment had to be stopped after three months because of symptoms of gastric ulceration. In general, treatment with cortisone is not always successful and sometimes the condition recurs when the treatment is stopped. In addition, it must be recognized that administration of cortisone for long periods may lead to an impaired stress reaction, and this may persist for up to two years after the cessation of therapy. Finally, no long-term results have yet been reported following drug therapy, while Stein (1956) has shown that improvement after wedge resection of the ovaries normally persists for the remainder of the patient's reproductive life. In consequence, wedge resection of the ovaries has been preferred as the method of treatment in this series. Operation has the added advantage of excluding the presence of a small masculinizing tumour which could not have been diagnosed otherwise (Siganos, 1961).

At laparotomy a simple wedge of one-third to one-half of each ovary was removed, the cut extending into the hilus; through this incision the numerous subcapsular cysts were punctured. If the ovary was greatly enlarged more tissue was removed so that the reconstituted organ was approximately normal in size. The defect was closed with a catgut suture.

Other forms of ovarian surgery which have been reported to be effective are stripping of the capsule, splitting of the ovaries, or a simple cut into the ovarian substance. Some leave the ovarian wedge everted in order to assist future ovulation (Bailey, 1959), but this has been found unnecessary. It is regarded as undesirable because bleeding from the cut surface may be difficult to control and there is an increased risk of subsequent adhesions.

No patient in this series had any major post-operative complication and all had left hospital within two weeks of the operation.

Results

All the 30 patients who had wedge resection from January 1958 to July 1961 were followed up in April and May 1962. The results of the treatment are shown in Table III.

TABLE III.—Results of Treatment

| | Improved | Not Improved |
|---|---------------|--------------|
| Absent or infrequent periods | 27 | 3 |
| Hirsutism | 4 | 23 |
| Obesity | 4 | 5 |
| Fertility (16 married patients) | 7 pregnancies | |

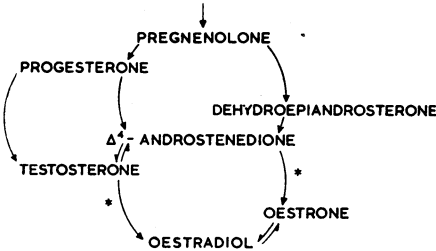
The results indicate that wedge resection helps to restore regular menstrual function and ovulation but has little effect on the abnormal hair or the obesity. This is in agreement with most of the results so far reported. It is too soon to attempt to assess the long-term results in this series.

Pathology.—The ovarian tissue removed was examined histologically. Macroscopically, multiple cysts were found in every specimen; however, the microscopical features which have been described in association with this syndrome (thickened

tunica and hyperthecosis) were not consistently present (Roberts and Haines, 1960).

Discussion

The following simplified scheme shows some of the normal pathways by which oestrogens are synthesized in the human ovary:



(The significance of the asterisks is explained in the text.)

Recently micro-analytical studies of the cyst fluid from ovaries of non-hirsute patients and those with the Stein-Leventhal syndrome have been carried out.

Giorgi (1962) compared the steroid concentrations in the cyst fluid of patients in our series with the concentrations in fluid from patients in whom polycystic ovaries were associated with other gynaecological disorders. Examples of the results in these two groups are shown in Figs. 3 and 4. In nearly all the patients

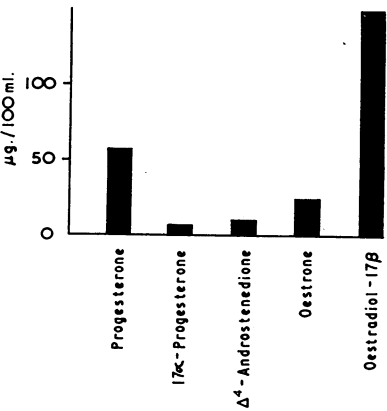


FIG. 3.—Steroid analysis of cyst fluid from ovary of patient not having Stein-Leventhal syndrome.

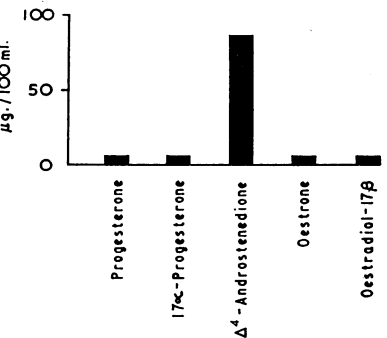


FIG. 4.—Steroid analysis of cyst fluid from Stein-Leventhal ovary.

with hirsutism and absent or infrequent periods oestrogens could not be detected in the cyst fluid and a high concentration of Δ^4 -androstenedione was found; the concentration of Δ^4 -androstenedione was higher in the patients with amenorrhoea than in those with oligomenorrhoea, but could not be related to the degree of hirsutism (E. P. Giorgi, personal communication, 1963). In patients with polycystic ovaries but without

these symptoms the follicular fluid contained some oestrogen and a lower concentration of Δ^4 -androstenedione.

These results confirm and extend previous studies upon cyst fluid by Short and London (1961) and Short (1962). These findings are an interesting corollary to previous studies upon ovarian tissue. Thus elevated concentrations of Δ^4 -androstenedione were found in some ovaries from Stein-Leventhal cases (Mahesh and Greenblatt, 1961, 1962), and a higher conversion of progesterone to Δ^4 -androstenedione has been demonstrated in the ovaries of patients with the Stein-Leventhal syndrome (Warren and Salhanick, 1961; Axelrod and Goldzieher, 1962). It is possible that one or more enzymic blocks occur in the pathway of steroid biosynthesis, but perhaps the most consistent defect involves the formation of oestrogens from androstenedione and testosterone. This would occur at the points indicated by an asterisk on the scheme and would lead to an accumulation of androgens and a deficiency of oestrogens. Such a block could be primarily ovarian or secondary to an endocrine abnormality elsewhere. The fact that ovarian surgery usually ameliorates the complaint is not proof that the ovary is the primary seat of the disorder, for an endocrine "feed-back effect" to the pituitary or adrenal may operate as a consequence of ovarian surgery. It is possible that an enzymic block of this nature is due to a chromosomal defect, and recent work (Netter, 1961) has shown genetic abnormalities in three out of eight patients with the Stein-Leventhal syndrome.

Wedge resection of the ovaries failed to restore cyclical menstruation in three patients. A retrospective analysis of the clinical features and special investigations of these patients revealed nothing which might help to differentiate them from the patients who responded to this treatment. (Estimation of Δ^5 -triol and vaginal cytology was not performed in these cases.)

Stein and Leventhal described the features of their syndrome, and while some of our 30 patients fall into this category some differ from the classical concept in the following ways:

1. Stein and Leventhal consider this to be an anovular condition. In 12 of our patients there was evidence of corpora lutea in the wedges of ovary removed and, further, both basal temperature charts and vaginal smears confirmed the occasional occurrence of ovulation before treatment.

2. Enlarged ovaries were palpable in only one-third of our cases prior to laparotomy, and at operation not all the ovaries were enlarged. Most of the patients had normal breasts and their uteri were not hypoplastic.

3. It is considered that the Stein-Leventhal ovary is not a specific pathological entity, and that changes so far described in these ovaries may occur in ovaries of other gynaecological disorders (Montgomery *et al.*, 1959; Haines and Taylor, 1962).

Because the clinical and pathological features of this syndrome are not entirely characteristic, it is to be hoped that the situation may be clarified in terms of underlying defects in ovarian steroid production. Raised levels of androgens from the ovary may give a widely varying clinical picture, depending on the amount and nature of the specific androgen, the duration of its action, and on the patient's age and tissue response to the androgen. The deficiency in oestrogen synthesis by the ovary may also be important in determining some of the clinical features of the

patients, and we consider that the variation in the clinical features of the patients in the present series will be fully understood only when the type of abnormal ovarian steroid synthesis is defined in each patient.

Summary

A study is presented of 30 patients with hirsutism and amenorrhoea or oligomenorrhoea, in 27 of whom regular menstruation was restored by wedge resection of the ovaries.

The clinical features of the patients differed from the Stein-Leventhal syndrome in several respects—that is, there was evidence of ovulation in at least 12, the breasts were usually normal in size, the uteri were not hypoplastic, sometimes the size of the ovaries was normal, and their microscopical features were not constant.

Treatment by wedge resection of the ovaries was regarded as preferable to hormone therapy, and it has the added advantage of excluding a small masculinizing tumour of the ovary.

Determination of steroid concentrations in cyst fluid revealed a defect in the synthesis of oestrogens in the ovaries of these patients, with an accumulation of excess amounts of Δ^4 -androstenedione in the cyst fluid.

The clinical features of these patients may be related to defects in the synthesis of the ovarian steroids.

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